(3435) Edwards (review)			
(3602) Edwards (review)			
(3838) Edwards (review)			
(3121) Peet	56M; 10F	30% coal miners 17% industry laborers	
(3221) Kerley (review)			x-ray diagnosis
(3222) Brockbank	52M*;10F	18 gas and fumes, 9 dusty jobs, 13 non-smokers, 9 smoked twist, 9 heavy smokers	4 war gas
(3534) Dudgeon & Wrigley	53 (? gender)		sputum wet film
(3329) Roberts	9M	tobacconist, carter carman, roadman, laboratory techncian	X-ray treatment
(3436) Dible	3M; 1F	3 stone mason 1 soapstone worker	silicosis
(3446) Ellis	4M; 1F	laborer, carter mason	cocaine and morphine treatment
(3437) Hill (review)			
(3438) Sears	23M; 3F		cocaine treatment
(3439) Young	1M	caisson sinker	surgery
(3440) Scadding	1M		radon treatment
(3535) Matheson	1M	carman	pericardial metastasis
(3628) Wood	13M; 1F		surgery
(3629) Holmes	4M; 1F		diagnosis
(3635) Bush	6 (? gender)		X-ray
(3630) El Gazayerli	79M; 16F		66 oat cell, 28 adeno-carcinoma or squamous
(3726) Tchaperoff	41M; 5F		X-ray treatment
(3727) Ormerod	92M; 8F		62 squamous cell 38 nonsquamous
(3728) Craig	3M; 1F		osteoarthropathy
(3729) Alexander	1M	transport driver's mate	19 year old oat cell
(3839) Allison & & Stanbury	2M	miner	surgery
(3840) Barrett	110 (? gender)		37 sputum positive 31 sputum negative
(3841) Brock (review)			surgery
(3842) Owen et al	5M; 2F	railway checker, tram driver, carpark attendant, butcher, forwarding clerk	apical tumor
(3843) Pilcher (review)			
(3844) Pilcher (review)			
Italy			
(3536) Becchini	10M; 1F		translation needed ?
(3103) Verga & Botteri	22M; 8F		translation needed ?

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Sweden (3837)	Westermark	55 (? gender)	X-ray patterns

* Tobacco Use

The articles indentified as Review are on the following subjects: diagnosis by symptomatology, radiology, bronchoscopy, clinical management, surgical treatment and microscopic features of lung cancer.

Apparent and Absolute Increase in Lung Cancer?

During the 1930's, proponents of causal association relied on the coincidental increases in male lung cancer incidence and in male smoking prevalence. Harris based his opinion on his interpretation of the literature:

> "5.1. During the period prior to World War I, pathologists, clinicians and vital statisticians began to note an increase in lung cancer - a disease that was relatively obscure prior to 1900. By the late 1920s and 1930s, a dramatic increase in primary lung cancer, predominantly among males, was recognized throughout the United States and Europe. Lung cancer began to overtake cancer of the stomach in clinical and autopsy series and in vital statistics analyses.
>
> 5.2. At the start, there was controversy concerning the genuineness of the increase in lung cancer incidence. Alternative explanations emphasized improved methods of diagnosis, increased autopsy rates, population aging, changes in disease classification and generally enhanced cancer awareness among physicians. However, such explanations did not accord with other facts, including the increase in the age-specific incidence of lung cancer, the disproportionate rise in lung cancer among males, the rise in lung cancer relative to cancers of other internal organs, and the increased proportion of lung cancers seen at autopsy. Beginning in the late 1920s, a growing number of pathologists, surgeons, vital statisticians, and other scientists realized that, at least since 1920, the rise in lung cancer was genuine, both relatively and absolutely.

During the deposition, Counsel selected the phrase "disproportionate rise in lung cancer among males" for clarification, using the complex and long 1936 article by Kennaway and Kennaway. A simplier approach was to have gone one

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step backward and challenge whether "the rise in lung cancer was genuine both relatively and absolutely."

Harris used the following articles to support the above summary statements: Perret (2711), Hoffman (2911),(3131), Mertens (3031), Arkin & Wagner (3613), and Kennaway & Kennaway (3632). These articles discussed under Topics C, D, and E, contain statements that question Harris' interpretation. Other Harris' references for his statement 5.2 are discussed in Chapters 4 and 5: Müller 1939, Ochsner & DeBakey 1939, 1941, Menne & Anderson 1941, and Graham 1951. In addition to the above references cited by Harris in his SOA 5.2, there are two comprehensive reviews missed by Harris. Simons, in his monograph entitled Primary Carcinoma of the Lung, stated:

> "It is apparent that the evidence permits of no other conclusions than these: first, that incidence of the disease has increased both absolutely and relatively; second, that continued suggestions that such an increase in only apparent and not real are rebuked by the facts; third, that the increase was gradual until the early 1900's, since when the gradient of increase has become constantly steeper; finally, that in many localities the greatest incidence seems to have been reached in 1924, while in others the frequency still is advancing." (pages 50-51 of ref. 3702)

Rosahn, in his 1930 review article entitled "The Incidence of Primary Carcinoma of the Lung", wrote the following:

> The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute. Combined statistics show that primary carcinoma of the lung at autopsy from 1910 to 1919 comprised 0.44 per cent of autopsies, and 4.39 percent of all cancers. Since 1920, primary carcinoma of the lung at autopsy comprised 0.89 per cent of autopsies and 6.98 per cent of all cancers. Primary carcinoma of the lung is not as rare as was formerly believed. (pages 809-810 of ref. 3020)

The two reviews generally agree with Harris' interpretation. However, British and American authorities question interpretation of Simons and Harris.

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British authors who question "absolute increase".

The situation during the 1920's and 1930's was confusing because an increase in incidence, whether relative or absolute, was denied by Passey and Holmes (3537) and Bonser (2845, 3458) from the University of Leeds. Davidson, from Brompton Hospital, detected an increase but was preoccupied with comparison to German statistics instead of analyzing whether the increase was relative or absolute (3003). Kennaway & Kennway (3632) compared the incidence of lung cancer with those of prostatic cancer reported by Moore (3538). They also discussed the possible factors which might have caused increase in lung cancer deaths:

> The increase in recent years in the number of deaths attributed to cancer of the lung may be due to one, or more than one, of the following factors: (1) An increase in the actual number of cases of the disease; (2) Improvement in diagnosis, whereby a larger proportion of the actual number of cases is detected in life; and an increase in the number of autopsies performed; (3) A tendency to identify as cancer of the lung cases which are really of a different nature; that is, a fashion in diagnosis. These three possibilities may now be considered in detail.
>
> (1) An actual increase. It is obviously difficult to obtain any direct evidence of this factor; one is driven to seek for indirect evidence by means of enquiry, how far the second and third factors can be excluded. The actual number of cases of any form of cancer must depend upon the size of the population of the country, and upon the distribution of age and sex within this population. But the increase in recorded cases of cancer of the lung is too great to be accounted for by any such influences. The dissemintion of tar from roads has been thought to be a factor which must produce an increase in cancer of the lung.
>
> (2) Improvement in diagnosis. The methods of examination of the lungs, and the provision of apparatus for such purposes, have undergone very great development in the last fifteen years, and it would be remarkable if these changes had not increased the number of cases of cancer of the lung detected. Hence there can be no doubt that this accounts in part for the apparent increase in the prevalence of cancer of the lung, but the question remains,

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whether a real increase is occurring also. If improvement in diagnosis is the whole explanation of the sharply rising curve in Graph 2 then over 1000 deaths from cancer of the lung in men in 1930 must have been ascribed to other diseases (see the figures for 1930 (1056 deaths) and for 1934 (2095 deaths) in Table XII. Obviously this factor will cease to act when the methods of diagnosis, and their availability to the whole population, cease to improve; hence it will be of great interest to see the changes in the prevalence of cancer of the lung in, say, the next 10 years.

A comparison of the prostate with the lung in this respect is of interest. Cancer of the prostate has shown a rate of apparent increase (Graph 4) which is very similar to that of cancer of the lung in males. The graph shows the recorded deaths from these two forms of cancer in England and Wales for the 24 years 1911-34. The number of cases of cancer of the lung remains at a very constant level of about 250 during the period 1911-19, and then shows a rise of increasing steepness to more than eight times that figure, or 2095, in 1934. The deaths from cancer of the prostate show a more uniform increase, though here again there is a tendency for a more rapid rise to set in during 1918-20; the last figures available, namely those for 1932-3-4 (Table XIV) indicate that the increase is coming to an end.

Recent investigations have shown that areas of tissue regarded as malignant can be found at autopsy in a high proportion of prostates, if a sufficiently minute search be made. There is thus in the case of the prostate a reservoir of malignancy which is drawn upon in proportion to the thoroughness of the examination, and it is probable that the same is true of the lung.

Passey and Holmes (3537) in an elaborate study for the years 1894-1928 of the numbers of intrathoracic neoplasms in relation to admissions to sixteen hospitals, found an increase in such tumours in five hospitals only of the sixteen, and these authors conclude that the reader 'will find it difficult to make out a serious case for any appreciable increase in the incidence of intrathoracic neoplasia in the period 1894-1928 ...'. This may be so, but it is difficult to see why the recent great increase in certification of deaths from cancer of the lung did not take effect upon more of the hospitals dealt with by Passey and Holmes, for one cannot suppose that the diagnoses in these institutions in, say, 1919, left no room for improvement.

(3) Fashion in diagnosis. The suggestion has been made that there is now a tendency to identify as cancer of the lung cases which are really of a different nature. If this factor is to account for the present form of the curve (Graph 2) one must suppose that every year medical men diagnose two or three hundred more cases wrongly; it will be interesting to see for how many years this course of action persists so as to maintain the curve

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> in its recent shape. Also, there must be a sufficient supply of patients who have intrathoracic conditions which are not cancer of the lung but are sufficiently severe to cause death. It seems very unlikely that this third factor can have any large influence upon the figures in question." (pages 255-257 of ref. 3632)

Since the existence of an increase in both males and females was uncertain, it was more difficult to analyze comparative increases in males and females. It was therefore not surprising that Harris' deposition relating to Kennaway & Kennaway appeared to be frustrating for both parties (DTH 607, Exhibit 62; SOA 131; Exhibit P131). In the Transcript of Proceeding, Harris was questioned about the contents of article by Kennaway & Kennaway (pages 1566-1567). The line of questioning was <u>percentage</u> increases in males compared to females, which to Harris "in percentage terms, what that meant when I read it, I was never sure."

<u>American authors who question "reality of increase in lung cancer incidence"</u>.

During the 1930's, several American monographers concluded that the statistics <u>did not</u> support the concept that there was a real and absolute increase in incidence of lung cancer. Instead, they proposed that there was a relative increase as a result of several factors that are described in the following quotations by Monographer (k) Fried, an internist from Minnesota:

> "The lack in the past, of knowledge of this condition, plus the unreliability of cancer statistics in general, considerably weakens the statement that bronchiogenic cancer occurs now more frequently than formerly. However that may be, as the problem stands, this point is apparently not susceptible of proof one way or another, and, therefore, no sweeping conclusions should be drawn.
>
> The author is of the opinion that the more frequent occurrence of this disease in recent years, as compard with older findings, can be explained on the basis of the following factors: (1) Improved clinical and pathological methods of diagnosis; (2) Increased attention to this malady (as Goethe has expressed it:

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> Man sieht nur was man weiss"); (3) Increase in span of human life (a much greater proportion of people reach the 'cancer age'). The increase, then, is very likely more apparent than real. (page 13, ref. 3201)

Additional quotations from Fried are included under Topics C and D. The opinions of other internists are in the next paragraphs.

Monographers (d) Hruby and Sweaney, in their review entitled "Primary Carcinoma of the Lung with special reference to incidence, early diagnosis and treatment", recalled the following figures:

> In all there are 1,355 cancers of the lung and 22,712 cancers in 185,434 autopsies. By adding the redistributed figures of Junghanns, Probst, Holzer, Derischanoff and Zacherl, who gave the numbers in five year periods, the results were almost identical, giving a total of 2,359 cancers of the lung and 38,338 cancers in 359,389 autopsies, perhaps half of all cancers of the lung reported to date.
>
> These figures and charts reveal a gradually increasing incidence of general cancer of around 65 per cent over the thirty-four years with a depression during and after the war. There is also an increasing incidence of cancer of the lung that is greater than the incidence of general cancer until the war; then, after a slight depression, there is a tremendous rise, the peak being reached in 1928, amounting to a tenfold increase. Since then there has been a tendency to decrease. Corresponding to this rise, however, is an increase in the diagnoses of cancer of the lung, as given by certain authors, from 5 per cent in 1896 to about 50 per cent in 1925. With careful work, it should approach 75 per cent at the present time. General cancer is entirely different. The diagnosis in this group should have been well over half correct throughout the whole thirty-four year period. Instead of a tenfold increase in diagnoses, as with cancer of the lung, there is no more than a 10 or 15 per cent increase.
>
> It may be contended that an increase in diagnoses should have no effect on figures based on autopsies, but it will tend to bring more cancers of the lung to autopsy and to increase the figures based on autopsies at the expense of the greater group of cancers of the lung that do not come to autopsy. Furthermore, the tendency to more hospitalization, better transportation, better training of physicians during the war and a better appreciation of medical aid on the part of the returned soldiers will increase the recorded incidence without affecting the true incidence of cancer of the lung.

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The causes of the increase in diagnosis of cancer of the lung are many and variable. In this regard, one must bear in mind that the discovery of the tubercle bacillus in 1882 permitted a vast number of patients to be separated from those definitely tuberculous and has made further search of diagnosis necessary. It has been our observation that tubercle bacilli are found in all but a trivial minority of active, advanced cases of pulmonary tuberculosis.

The discovery of the x-rays in 1896, with their far-reaching application in medical diagnosis in the last twenty years, has also established the diagnosis of cancer of the lung in many patients whose disease would otherwise have been classed as some other condition.

The use of opaque substances (iodized poppy seed oil 40 per cent), bronchoscopy, pneumothorax, thoracoscopy and bronchoscopic section have all added to diagnostic equipment until over 75 per cent of the diagnoses of cancer of the lung today are, or should be, correct, while less than a decade ago Staehelin, Kikuth, Wells, Grove and Kramer and others reported not over 35 per cent correct diagnoses. Ferenczy and Matolcsy reported 5 per cent correct diagnoses from 1896 to 1900, 28.4 per cent from 1917 to 1925, and 50 per cent in 1925. In Lubarsch's series, the correct diagnoses totaled 52 per cent in 1920. In 1913, Weller reported only 11 per cent in a collected series of 90 cases. These figures show a marked improvement in diagnosis as years go by.

This same principle applies to nearly all internal and 'inaccessible' cancers, although the incidence of external cancers has changed little - in fact, the death rate from external cancer has decreased.

More important than any other factors, however, is the change in pathologic diagnoses. Pathologist have varied their attitude toward the nature of cancer of the lung, thereby placing many cases in this group that were formerly considered to be some other condition. As pointed out by Fried (3201), a dictum of Virchow pervaded the field for a long time. Virchow was of the opinion that the tissue which was subject to metastatic growth rarely produced primary growth, and the lungs were cited as an example. Only a few scattering reports came from the early writers, and perhaps not until Virchow's great influence began to wane did the subject again become open to unbiased investigation. Many of the cancers found in the lungs were formerly considered to be metastases because they are chiefly located at the hilus, where metastases commonly occur. Many were also considered as mediastinal tumors.

One of the greatest changes, however, from the pathologists' point of view, was due to a better understanding of the origin of the undifferentiated cells in cancer of the lung, many of which were formerly considered sarcomatous.

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> Some of the small cell and even the 'oat cell' types may have been considered as sarcomas. In Hunt's series of 26 cases, 21 were of the 'oat cell' type. Then many were perhaps considered mediastinal tumors (lymphosarcomas, thymomas and similar tumors) without careful histopathologic analysis. So one sees that it is not only an improvement in diagnoses but the change of erroneous diagnoses in a relatively small group of cases that come to autopsy that may well have produced a tremendous change in the apparent incidence of cancer of the lung." (pages 504-506 of ref. 3302)

The data cited above were derived mostly from German publications and compared with American and British statistics. The overall interpretation by Hruby & Sweaney is that this increasing incidence was due to improved diagnosis.

Monographers (f) Frissell & Knox, in their 1937 article entitled Primary Carcinoma of the Lung stated:

> It is obvious, then, that primary carcinoma of the lung is not the rare disease it was formerly believed to be, but the question as to whether the increase is actual or apparent is still open to debate. The following observations must be taken into account. First, many tumors classified as sarcomata by pathologists of the last century are now included as epithelial tumors of the so-called oat-cell variety. Secondly, carcinoma of the lung, when found, was usually considered metastatic; this resting on the statement of no less an authority than Virchow, who stated that organs in which epithelial tumors metastasized were rarely the seats of primary carcinoma. Third, the widespread interest of pathologists in this subject, particularly in the last decade, has led to the discovery of a considerable number of small pulmonary neoplasms with large metastases; such metastases earlier observers undoubtedly regarded as the primary lesion. Clinically, there is no question that our newer methods of investigation - roentgenography with or without lipiodol, bronchoscopy, thoracoscopy, etc. - have led to frequent ante-mortem diagnoses, whereas in the early literature the diagnoses were almost exclusively post-mortem. Since external and readily diagnosed cancer has not increased, it would seem probable that, in spite of the evidence of the post-mortem figures, especially in Germany, the increase in the incidence of bronchial carcinoma in the last two decades is apparent rather than real. Our own statistics seem to agree with the other in indicating a general rise, whether or not it be an actual one. (page 220 of ref. 3705)

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The above quotations are repetitive but are useful in emphasizing that the claim of an absolute increase in lung cancer incidence was questioned by American physicians.

Monographer (g) Klotz represented the opinion of some pathologists that interpret the increase incidence as apparent rather than real or absolute:

> "Nearly all are agreed that the condition is encountered with greatly increased frequency, and this has raised the controversial question of whether the increase is actual or apparent. In a survey of much of the European literature on the subject, Bonser found a reported increase in the condition in 32 instances, a slight increase in 5 and no increase in only 8. Wahl from 1895 to 1927, found an increase in the incidence of cancer of the lung from 0.44 to 1.69% of all autopsies; Duguid, from 1885 to 1926, observed an increase from 0.24 to 2.57%; Kikuth, from 1889 to 1923, showed an increase from 0.02 to 0.86% and Barron, from 1889 to 1921, an increase from 0 to 0.9% and so on. The increased frequency with which the disease is recognized is further emphasized when one considers that Adler (1201), was able to collect but 374 authenticated cases, whereas a complete present-day summation would number thousand with some reports, including a hundred or more from a single source. A few investigators believe that no increase has occurred in the incidence of carcinoma of the lung. Thus, Bonser (3458) was unable to demonstrate any change in the incidence of the condition in relation to total autopsies, total cancers, or hospital admissions at the Leeds Infirmary. Though this worker did observe that the highest incidence occurred durng the 5-year period ending in 1932, this was only slightly in excess of the incidence for the 5 years from 1908 to 1912. Similarly, Passey and Holmes (3537), in a carefully controlled analysis of the available statistics from some of the teaching hospitals of Great Britain, found no increase in the incidence of carcinoma of the lung in 8 instances and a variable increase in 8 others. These writers considered that the increased incidence found in these latter was the result of special circumstances and did not indicate a real change. The statistics from several of these hospitals, from which it was deduced that no increase had occurred, had previously been reported in a different form and had been considered indicative of an actual increase.
>
> Despite such reports as the foregoing, the great majority of authors are agreed that the condition is now seen more commonly than formerly. Most of them, however, consider the increase purely apparent and offer a variety of reasons in explanation of this. Important among these are the increased span of human life, and increased interest in the condition stimulated by both improved diagnostic equipment and the hope of carrying out

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> successful intrathoracic surgical procedures. Other important factors are fashion in diagnosis, and the changed attitude of the pathologist who now recognizes to be actually primary carcinoma pulmonary lesions formerly considered metastatic, sarcomatous or inflammatory." (page 440 of ref. 3802)

William Boyd, prior to writing a Textbook of Pathology, published an articled entitled "Some Reasons for the Recent Increase of Bronchial Carcinoma":

> "Let us now retrace briefly the steps that we have taken in our inquiry. We have seen that there are a number of factors each of which has contributed in turn to the sum total of cases of bronchial carcinoma which are recognized at the present day. Of these by far the most important is the truth contained in the saying: 'What we know, we see'. That is true of coronary thrombosis and it is true of bronchial carcinoma. It is true, moreover, for the clinician, the bronchoscopist, the radiologist, and the pathologist. The eyes of the first three have been opened by the observations of the pathologist. The pathologist's myopia is the most difficult to explain. It may be accounted for in three ways. (1) The gross lesion may closely resemble other neoplasms or may be obscured by changes secondary to bronchial obstruction. (2) Recent years have brought realization of the fact that carcinomas in general and those of the bronchus in particular vary greatly in their microscopic appearance and may closely mimic sarcomas and lymphosarcomas in this respect, so that even the microscope may fail to correct the error. (3) The natural history of the disease as illustrated by the behavior of metastases is highly characteristic, but the knowledge of this truth is of recent date. Without denying the possibility that there may be some real increase in the incidence of the disease, it is suggested that the various factors which have been discussed, coupled with the present increase in the span of life, are sufficient explanation for the apparent increase which has attracted the attention of observers in all countries - observers, however, who have had their eyes opened so that they can look-see as well as look, and who therefore see what they know." (pages 329-320 of ref. 3812)

The above comments by Boyd are essentially similar to an earlier article (3026). His opinion is unlike that of Ewing, another pathologist.

Although surgeons are presently against cigarette smoking, it is important to note that their publications in the 1930's did not reflect an

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anti-smoking attitude. Graham, Singer and Ballon, in their monograph entitled Surgical Diseases of the Chest, stated:

"Statistics. - There are many who are of the opinion that carcinoma of the lung is definitely on the increase. The following statistics reported by others are, therefore, presented in an attempt to see if the increase is definite or merely relative. M. Brandt (Riga) reports findigs in 13,179 necrospsies performed between the years 1901 and 1925. There were 828 cancers, 108 were primary in the lung. Between the years 1901 and 1905 the pulmonary cancers comprised 1 to 2 per cent of all tumors. Between the years 1916 and 1921 and 1925, pulmonary cancers comprised 10 to 11 per cent of all the cancers.

S. Wahl has reported the following statistics from the Municipal Hospital Moabit. During the years 1922 to 1927 there were 3372 autopsies. There were 57 cancers which were primary in the lung or 13 per cent of the cancers observed (438); during the years 1916 to 1922 there were 3342 necropsies, 396 cancers, 24 of which were primary in the lung (6.06 per cent).

Hanf, of the Charite, Berlin, has published (1903 to 1925) the statistics shown in Table 106.

Holzer of Prague has reported some statistics on cancer of the lung over the years 1895 to 1924. During the first ten years primary cancers of the lung comprised 1.04 per cent of all cancer, during the second decade 2.36 percent and during the third decade 6.69 per cent. There were more necropsies in later years and consequently more primary carcinomas of the lung, still the increase in primary lung tumors was apparent.

de Vries reported 39 carcinomas of the lung observed in 8000 necropsies. Twenty of these were seen during the period of 1922 to 1926.

Frenczy and Matolecsy of Vienna have reported most instructive statistics. Since 1925 there were 2,821 postmortems; 334 tumors, 24 primary in the lung or 7.2 per cent.

v. Zalka in 1928 published statistics from St. Stephens Hospital, Budapest, from 1894 to 1927. They showed that since 1904 the percentage of lung cancers relative to all cancers has varied very slightly. The maximum occurred between 1914 and 1918 (3.35 per cent). From 1919 to 1923 it was 2.67 per cent and between 1924 and 1927 the proportion has increased to 6.65 per cent.

The incidence of primary carcinoma of the lung is given by Weller who states that prior to 1900 the percentage of incidence of carcinoma of the lung at autopsy ranged between 0.57 per cent (Reinhard) and 0.428 (Wolf). The statistics compiled by Brunn are given in Table 109.

Reference has already been made to the increase in incidence of carcinoma of the lung in particular institutions. The reasons given for this increase are better methods of diagnosis, more correct diagnoses, recommendations of more such patients to the

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hospital, actual increase, etc. These various factors will be referred to again.

In reporting some interesting statistics on cancer Hoffmann (3131) has made reference to the reports published by the Census Office of the United States. In 1914 out of 52,420 deaths from all forms of cancer 371 were attributed in this report to cancer of the lungs and pleura. The equivalent proportion was 0.7 per cent but at a rate of 0.6 per 100,000 of population. Ten years later, 1924, the number of recorded deaths from cancer of the lungs and pleura was 1586 equivalent to 1.7 per cent but at a rate of 1.6 per 100,000 population. Statistics for England and Wales for carcinoma of the lung and pleura during 1901 to 1910 was 1 per 100,000 of standardized population. From 1911 to 1920 the corresponding death-rate was 1.34; during the year 1926 it had reached 2.33. For Albany, New York, the rate for cancer of the lung for 1919-1923 was 2.5. For New Orleans during the same period it was 2.8 for white population and 0.6 for the colored. For Chicago it was 2.8 for 1924 and 2 for 1925. For British Columbia it was 2.1 for 1920 to 1924; for Saskatchewan during the same period it was 9.5, for the city of Winnepeg 3.3. Hoffmann was unable to find a single case which could be attributed to nicotine. (pages 808-811 of ref. 3502)

Graham, in his 1936 article entitled "Primary Carcinoma of the Lung or Bronchus", stated:

"One of the most discouraging results from the study of any large series of cases is the revelation that nearly all of them have been allowed to progress to an advanced state without so much as a suspicion in the doctors' minds of the true nature of the condition. One can forgive an attending physician for not establishing the diagnosis of bronchiogenic carcinoma because of the expert teamwork that is sometimes necessary. It seems difficult, however, to excuse him when he does not even take the possibility into consideration in a case of unexplained cough which has arisen insidiously in a patient of middle age or older. If the medical profession, as a whole, should appreciate the frequency of this condition, and the necessity and the desirability of taking prompt measures to establish the diagnosis in a suspicious case, probably a great many of the patients might be saved. It is a matter of the greatest importance that educational campaigns should be conducted to inform the general medical profession of the principal signs and symptoms suspicious of this condition and to get them to appreciate that bronchiogenic carcinoma is so frequent that its possibility must always be considered when dealing with a patient with unexplained cough.

The change in the point of view of the profession concerning this condition is well illustrated in a recent experience of ours. From one small city of approximately 100,000 inhabitants not far

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increase in cancer incidence (3911). It is apparent that during the 1930's, the increased incidence was being questioned by Americans and Britishers, because the absolute increase was limited to the European continent.

Surgery of Lung Cancer.

One of the most significant development in lung cancer during the 1930's was the progress in surgical removal of the lesion. The first successful removal of an entire lung with bronchial carcinoma was reported in 1933 by Graham and Singer (3319). Graham's publication (3617) and his monograph (3502) are discussed above, and his later publications are reviewed in Chapters IV and V. There was no statement in the 1930's that Graham suspected tobacco smoking as a cause of lung cancer. His accomplishments were the subject of an editorial of the Journal of Missouri State Medical Association (3442). Churchill, Overholt and colleagues, attracted surgical residents to Boston which soon became a center for pulmonary surgery (3314, 3315, 3419, 3420, 3520, 3521, 3614, 3615, 3714, 3821, 3822, 3921, 3922, 3923).

Reinhoff and his collaborators at Johns Hopkins Hospital improved further on the surgical treatment of lung carcinoma (3418, 3633, 3634, 3935, 3949). They developed a two-staged operation for pneumonectomy which did not become popular because of successful one-stage lobectomy introduced from Great Britain (3439, 3841). Dolley and Jones wrote a comprehensive review of lobectomy (3936). I examined most references and could not find any secondary citations used by Harris in support of his concept that cigarette smoking was a cause of lung cancer during the 1930's. In other words, chest surgeons, like Graham,

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were not convinced that most of their lung cancer patients were also cigarette smokers (3553).

Bronchoscopy.

Jackson and Jackson from Temple University in Philadelphia improved on the visualization of bronchial passages by endoscopy. They introduced the instruments for direct bronchoscopy that contributed to early detection of bronchial carcinoma (3028, 3443, 3937). There was no mention of cigarette smoke as a cause of bronchial carcinoma. In their monograph entitled Cancer of the Larynx, the chapter on etiology listed 27 causes of laryngeal diseases, including alcohol, tobacco, dust, war gasses and other vapors. The pertinent paragraphs were as follows:

> "Tobacco. - Contrary to that of alcohol the effect of tobacco in producing chronic disease of the larynx is local not systemic. It is not the nicotine but the empyreumatic oil produced by the destructive distillation of the burning tobacco that causes the injury to the laryngeal mucosa. This injurious effect is not confined to the smoker himself but is noticeable in the larynx of anyone who remains long in a room whose atmosphere is saturated with tobacco smoke. Chewing tobacco, which used to be so common, is little if at all injurious locally; if injurious at all it is only by the effect on the general health. Tobacco smoking is one of the chief reasons for the enormous preponderance of men as compared to women afflicted with chronic laryngitis. Since the vice is becoming more prevalent among women this sexual difference in incidence may be lessened. Tobacco smoking is probably one of the minor causes of cancer of the larynx; it cannot be regarded as an essential cause.
>
> Alcohol. - As a clinical fact it has long been known that alcohol is a potent cause of laryngeal disease acute and chronic. It seems to be the impression that local irritation of alcoholic contact is the mechanism. This is a mistake; alcoholic beverages do not reach the larynx. Observation in thousands of patients justifies our opinion that it is the prolonged, peripheral, vaso-dilator effect of alcohol that is so injurious to the laryngeal mucosa. The mucosa of the larynx of the victim of alcohol, who used to be so common before the days of prohibition, was always engorged. It was evidently the chronic engorgment of the cords

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> that was responsible for the hoarseness. The engorgement is noted within twenty mintues of the taking of a single drink of whiskey, but if not repeated the engorgement subsides within a few hours. It is the constant repetition of the alcohol that results in the vasomotor condition resembling paralysis and the chronic engorgement. This 'whiskey voice' is a form of hoarseness that disappeared from the United States during the prohibition period. At the present rate of advertising of the liquor interest and the hotels and restaurants, the development of a new group of addicts to the vice of chronic alcoholism is only a question of time. Those who prided themselves on the art of dining, which meant a different wine between each course, had the 'whiskey throat'. It is possible also that 50 per cent alcohol as in undiluted whiskey or brandy in passing over the extrinsic laryngeal mucosa may cause some congestion of this area that might extend to the upper posterior intrinsic area. Dilution of alcohol hastens the vasodilator effect. Total abstinence offers the only hope of retaining a normal laryngeal mucosa. Singers should be warned of this." (pages 51-53 of ref. 3704)

The above quotations appeared in the 1937 Edition of the Jackson & Jackson monograph. The 1939 Edition cited as Exhibit P385 by Harris is not available in New Jersey at the time of preparation of this chapter. Ms. Thompson will compare the above with Chapters XXIII and XXIV mentioned by Harris.

Cellular Origin of Malignancy and Classification.

Although several systems of classifying lung cancer were introduced, Ewing favored grouping according to histogenetic origin, namely: (a) bronchial epithelium leading to squamous cell carcinoma; (b) bronchial mucous glands leading to adenocarcinoma; and (c) alveolar cell carcinoma (4001). Other pathologists disagreed on the alveolar cell origin and instead favored major grouping into undifferentiated or small cell carcinoma, and differentiated including adenocarcinoma and squamous cell carcinoma (3023, 3029, 3424, 3523). Adenocarcinoma of the human lung had similar histologic appearance as adenomatosis or jaagsiekte in sheep (3938). Contrary to enthusiastic predictions,

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during the next forty years, the sheep disease proved to be inapplicable for research on human pulmonary adenocarcinoma.

The search for case reports was conducted as completely as possible to answer the fundamental question: What were the common etiologic factors subscribed to by clinical investigators of lung cancer during the 1930's? Since there were no computerized database, literature search was conducted visually and manually and I am certain that most significant publications were retrieved. Only 5% of 223 articles (4712 patients) contained information on smoking habits, and 15% contained information on occupational history. From these figures, it can be concluded that physicians writing case reports on lung cancer believed that occupational history was more important than tobacco smoking.

The coverage of lung cancer in the collected publications is not limited to etiology of lung cancer. Review articles on symptomatology, differential diagnosis, radiology and bronchoscopy are included. Treatments by radon implantation and surgery were introduced during the 1930's, with initially encouraging results. These case reports on lung cancer for this decade are more detailed than earlier or later ones. The work history are so varied that I could not find any pattern relating to geography, other than miners in areas known for producing coal and metals.

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C. TOBACCO USE AND LUNG CANCER

According to Harris, many surgeons, cancer specialists and other physicians reported that lung cancer patients were "almost always heavy smokers." In his State of the Art (Table 2), two were reported in the 1920's, ten in the 1930's, and nine in the 1940's. More than half were by foreign authors, and a third of these were by Germans. My plan is to discuss eight articles dating from 1930 to 1938. The 1939 publications by Ochsner & DeBakey and by Müller are shifted to the next chapter (IV) because supportive articles appeared during the 1940's. When World War II ended, it became apparent that Müller's followers, E. Schairer and E. Schveniger, from Friedrich-Schiller University in Jena, submitted collaborating publications in 1943 (at the time Hitler was over-running Euruope) under the sponsporship of the Scientific Instutitue for Research on the Dangers of Tobacco (4311). The possible relationship of this anti-smoking group to Nazi medicine is discussed in Chapter IV.

According to Harris, the tabulated contents of literature were useful in the following respects:

> "5.4. Beginning in the late 1920s, many surgeons, cancer specialists and other physicians, reporting their clinical experiences with this relatively new cancer, noted that lung cancer patients were almost always heavy cigarette smokers (Table 2).
> 5.5. During the 1930s and early 1940s, the proposition that cigarette smoking caused lung cancer received increasing scientific support (Table 2). Among the several lines of supporting evidence were the following.
> 5.6. The concept of cigarette smoking as a cause of lung cancer was consistent with the previously recognized link between pipe or cigar smoking and oral cancer.

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5.7. Further, while pipe and cigar smoking were linked with oral cancer, the widespread inhalation of cigarette smoke, it was reasoned, should be linked mostly to cancer of the lower respiratory tract. Such an hypothesis was supported by observations in cancer patients relating the site of cancer to the type of tobacco used.

5.8. Moreover, the rise in lung cancer in men parallelled the growth in male cigarette use. The relatively low incidence of lung cancer in women accorded with the delayed emergence of widespread cigarette smoking among females.

The above SOA statements was Harris' version of scientific events during the 1930's. Harris omitted mentioning the fact that most monographers on lung cancer omitted any consideration of tobacco hypothesis. Majority of authors of original publications favored other causes of lung cancer, and specifically denied importance to the theory initiated by Germans that tobacco was the cause of lung cancer.

Lung Cancer Monographers.

It was stated in the Introduction to this Chapter, that lung cancer monographers are the preferred authorities over authors that wrote books on cancer in general and who had not done original research in the field of lung cancer. There are about two scores of lung monographers listed above as Monographer (a) to (x); majority did not mention tobacco smoking as an etiologic factor. On the other hand, almost all of them included discussions of occupational/environmental exposure to fossil fuel products and combustion emission, and hostal factors influencing susceptibility to lung cancer. The pertinent quotations relating to tobacco-smoke are discussed in this subtopic, and those relating to other etiologic factors are discussed under Topics D and

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E. Contents of lung cancer monographs are distributed under several Topics so that conflicting issues are individually argued in the original written version.

Ewing's monograph was relied upon by Harris as the "sole" authority on lung cancer in general. Ewing allowed half a page on the subject of coal tar and tobacco-smoke, and his statement "the proportion of smokers among patients with lung cancer is very high," was accredited to Roffo. However, the bibliographic source was not mentioned (page 1115 of ref. 4001). This omission implies to me that Ewing hurriedly added Roffo to the page proof of the text, perhaps at the request of interested parties, because Ewing had not conducted research on etiology of lung cancer.

On the other hand, several lung cancer monographs contained detailed reviews of occupational/environmental factors and tobacco smoking as etiologic factors. I decided to quote the important sections so that the reader can recapture the mood of the monographers who were faced with conflicting opinions. Each monographer, after mentioning selected facts, made his own selection of preferred hypothesis. The choice was one, two, or all three of the following: first, personal habits, including diet and tobacco smoking; second, occupational and environmental exposure to fossil fuel, combustion emissions and other industrial carcinogens; third, hostal factors influencing susceptibility or predisposition to lung cancer.

Monographer (c), Simons: Primary Carcinoma of the Lung (3702). This 1937 monograph contained a review of the origin of the hypothesis that cigarette smoking was a suspected cause of lung cancer. Most foreign references that dated back to the 1920's have been collected for translation. A four-

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digit number, matching the Bibliographic Number of this Review, has been inserted into original quotations.

"Adler (1201) first noted that male cases exceed female and attributed the difference to irritation caused by tobacco smoking. One of the four patients whose cases were reported by Scott and Forman (1611) was exposed to both heavy tobacco smoke and heavy chemical vapors. Seyfarth (2421) allowed that inhalation of tobacco smoke may have more or less bearing on the origin of lung cancers. Berblinger (2529) admitted that smoking may be an additional causative factor in pulmonary cancers, and Fahr saw an increasing stimulus in the inhalation of cigaret smoke.

In 36 of his cases Hoffman (2911) found no evidence of absorption of nicotine; while among 29, 17 were excessive smokers, seven were cigar makers, one was a cigaret maker and the other smoked, but not to excess. In 17 cases the patients were women, concerning whom it was hard to determine the influence of smoking. Hoffman added Tylecote's information (2719) that in almost every case he saw or knew of the patient was a regular smoker, usually of cigarets; two of the exceptions were women who lived near railway stations where engine smoke continuously pervaded both houses and gardens and who succumbed unusually rapidly to the disease.

Ninety per cent of Arkin and Wagner's patients (3613) were chronic smokers, and these authors believed that inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi and bronchioles. Oberndorfer (2330) considered smoking and influenza the principle etiologic agents of bronchiogenic carcinoma. Vinson (3215) has merely noted the fact that 70 of 140 cases of carcinoma of the tracheobronchial tree were smokers. Owing to the amount of tar and methyl alcohol contained in tobacco, Ferrari (3331) considered smoking and important etiologic agent of lung cancer. He stated that in Trieste, where more tobacco is used than in any other Italian province, the incidence of pulmonary carcinoma is the greatest. Lickint (2931) cited reports indicating that cancer of organs within the so-called smoke tract - the lips, oral cavity, larynx and bronchi - is more frequent in smokers than in non-smokers. He showed that as the habit of inhaling the smoke increases, the incidence of bronchial tumors increases likewise. However, he conceded that not all bronchial cancers which develop in smokers are caused by tobacco but expressed the opinion that tobacco is the chief cause in a majority of the cases. In many cases the effect of tobacco concurs with other carcinogenic factors. He concluded that it cannot be doubted that tobacco smoke plays a role in etiology of bronchial carcinoma, as a result of which persons whose family history indicates a predisposition to cancer should be advised against smoking.

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> The mere fact, stated Staehelin (2526) that there are more men than women smokers and more male than female cases of lung cancer is not sufficient proof of the etiologic influence of smoking. Kikuth (2527), finding little history of smoking among his cases, believed that pulmonary carcinoma would have to occur much more frequently among those who smoke to excess before this could be regarded as a big factor. Katz's view - that in this connection one should keep in mind the Orient, where smoking has been practiced long and extensively - is scarcely pertinent since there are no figures from that source. If increased smoking were responsible for the assumed rise in incidence of pulmonary cancer, then, maintained Passey and Holmes (3537), carcinoma of the tongue, pharynx and larynx should have increased in incidence in proportion to the increase found in carcinoma of the lung.
>
> Tobacco smoke as a lung irritant may be considered among possible causes of pulmonary carcinoma but cannt be counted an important one in the present state of information." (pages 89-91 of ref. 3702)

In the above quotation, Simons questioned the opinion of Katz and simply reiterated the proponents of each side of the controversy. Simons concluded that tobacco smoke "cannot be counted an important one in the present state of information." A similar statement appeared in a 1935 article by Simons, two years prior to the appearance of the monograph:

> "Adler first noted that male cases exceed female, and attributed the difference to irritation caused by smoking. Berblinger (2529) admits that smoking may be an additional causative factor in lung cancers, and Fahr sees an increasing stimulus in the inhalation of cigarette smoke.
>
> The mere fact, says Staehelin (2526), that there are more men than women smokers and more male than female cases of lung-cancer is not sufficient proof of the etiologic influence of smoking. Kikuth, finding little history of smoking among his cases, thinks that lung-carcinoma would have to occur much more frequently among those who smoke to excess before this could be regarded as a big factor.
>
> Tobacco smoke as a lung-irritant may be considered among possible causes of lung-cancers, but cannot be counted an important one in the present state of information." (page 640 of ref. 3525)

Two years after the appearance of the monograph, Simons continued to make the statement that "trauma, general hygiene, roentgen rays, the inhalation of dust,

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tar particles, motor exhaust fumes, war gases and tobacco smoke may each be responsible for a very few of these neoplasms, yet proof that any one of them is etiologically significant is lacking" (3824).

Monographer (o), Davidson: Cancer of the Lung and Other Intrathoracic Tumors. The discussion of etiology was highlighted by the following paragraphs:

> "The aetiology of primary lung cancer, which has been the subject of so much speculative investigation in the last few years, is at once the most urgent and the most difficult matter. Apart from the coventional consideration of figures relating to age and sex incidence, questions of heredity, trauma, occupation, and so forth, which naturally form a basis for the aetiological discussion of most cancer problems, the peculiar increase in this special form of the disease - and this we are assuming to be a genuine fact - has led to a vast amount of inquiry, with the result that numerous theories have been advanced, mostly relating to the factor of irritation in some form or another of the respiratory literature on this subject gives the impression at first that considerable number of cases have been investigated, this is perhaps somewhat fallacious. A good many of the statistical observations on this point have been duplicated, to say the least of it, and furthermore it needs but the most elementary knowledge of statistical work to enable us to realize that a far greater bulk of facts must be available before it will be possible to draw conclusions of any real scientific value.
>
> One of the regretable obstacles to the pursuit of truth is the fact that human nature is prone to grasp at straws, and nowhere is this more apparent than in the history of medicine, especially in those branches of it which deal with the causation and treatment of great national scourges such as cancer and tuberculosis. It must therefore be remembered, in discussing the various suggestions that have been put forward to account for the increased incidence of new growths of the lungs and bronchi, that we are dealing with a subject the intrinsic difficulty of which is that of the aetiology of cancer generally, and that in respect of the various conditions producing irritation, no sufficiently large mass of reliable facts has so far been collected to enable us to deduce any real principle of cause and effect. With this preliminary caution, it is of some importance to consider the various points which have been put forward by different observers.

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> Tobacco, war gas, petrol fumes, dust, and tar from the roads have all been subject to discussion as possible and likely sources of irritation, but it cannot be said that any observations have been made so far which justify definite conclusions as to the aetiological importance of these factors, and such control evidence as there is does not lend much support to the theories in its favour." (pp 31-34, ref. 3003)

It should be noted that tobacco and other inhalants are covered in one sentence as "possible or likely sources of irritation." Davidson, unlike Simons, subscribed to the primary importance of hostal factors influencing susceptibility.

Monographer (g), Klotz: Primary Carcinoma of the Lung. Klotz regarded each inhalant separately into tobacco smoke, dust from tarred roads, fumes from gasoline engines, and pollution of the air in industrial centers, and dusts in mines. The discussion on tobacco smoke was critical of Hoffman and McNally, highlighted in Harris' SOA report:

> "The alleged increase in the incidence of lung tumors has resulted in an analysis of the habits of modern civilization in the hope of discovering some predisposing factors. Thus, smoking of tobacco, exposure to dust from tarred roads and the inhalation of fumes from gasoline engines have all been incriminated. McNally (3224) suggested that nicotine, phenol bodies, pyridine bases and ammonia, contained in cigarette smoke, were irritants which could account for 'cigarette cough,' chronic bronchitis, leukoplakia and the recorded increase in cancer of the lung. Hoffman (3131), on the basis of elaborate and confusing statistics, concluded that smoking habits unquestionably increase the liability to cancer of the mouth, esophagus, larynx and the lungs. Hoffman adds the astounding statement that non-smokers are subjected to the same dangers owing to air pollution by smokers. However, it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank (3222) found but 14.5% of his cases heavy smokers, while 21% were non-smokers. Furthermore, if smoking were a factor of any importance it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women." (page 450 of ref. 3802)

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On the other hand, Klotz was less critical of the role of coal tar and fossil fuel combustion products. There was a third group of monographers who were critical of the role of tobacco smoke but more so of coal tar, fossil fuel products and combustion emissions.

Tobacco Smoking versus Occupation/Environmental Factors.

Publications dealing on clinical observations on lung cancer patients usually incude a brief review of etiology. The scope of etiologic factors generally range from first, critical of tobacco smoking but less critical of occupational/environmental factors; second, critical of tobacco smoking and of occupational/environmental factors but favor hostal factors influencing susceptibility to lung cancer; and third, mention without criticizing tobacco smoking, occupational/environmental factors, and hostal factors. Those belonging to the third group are simply listed, but sample quotations for the first and second group of authors are included below.

Authors critical of causal association of tobacco smoking to lung cancer. Duhig, from Brisbane Hospital for Sick Children, (3220), agreed with an earlier article by Hueper that excluded tobacco smoke as an important cause of lung cancer (2933). Duhig also favored the causal importance of "atmospheric dust and in particular, dust containing known carcinogenic agents, tar from roads and that of a kind smilar to the notorious Schneeberg mine dust" (3220). Fennel, from Honolulu Clinic, stated that "inspite of a tremendous increase in the consumption of cigarettes by both sexes, no one has yet offered a good evidence that it plays a role in the etiology of lung cancer - that is a consolation to many middle aged physicians" (3612). On the other hand, Fennel

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expressed the opinion that "at present, the most dangerous irritation factor "is the use of automobiles on tar covered roads."

Donald S. King, from Massachusetts General Hospital, during the discussion of his paper entitled "Primary Cancer of the Lung," was asked to explain the high percentage of cancer of the lung in men and very low percentage in women. King's answer was:

> "I cannot answer that. No one, of course, knows the cause of cancer. Everyone has tried to discover some irritant of the respiratory tract which might be responsible. The use of tobacco is always mentioned as a possibility, but it has never seemed to me to be a satisfactory explanation." (p 833, ref. 3823)

Cecil V. King, from the Gallinger Municipal Hospital, D.C., discussed etiology in an article entitled "Primary Carcinoma of the Lung:"

> "The cause of carcinoma of the lung is similar to that of cancer elsewhere, particularly regarding inherent predisposition, age, race, etc. Irritation may be a factor, notably in certain miners who inhale radioactive dust. Also, pulmonary infections, such as influenza have been said to predispose to cancer of the lung. Tuberculosis is more common at an earlier age than cancer, so that these are not often found together. Recently, however, McNally (3224) has called attention to the fact that cigarette smoking has increased very much in the past 20 years, which increase parallels the rise in cancer; and it is possible that in some cases this source of irritation may be a factor. In the experience at this hospital cancer of the mouth has been seen quite frequently at the site where an old tobacco chewer has repeatedly held his tobacco. Certain it is, also, that cancer of the lung is found in the male about 3 times as frequently as in the female; but this is true also of primary carcinoma of the liver, Hodgkin's disease, and possibly other forms of malignancy." (page 37 of ref. 3413)

Warner, from the University of Maryland, was critical of the hypothesis that inhalation of tobacco smoke was the cause of high incidence in man - "no convincing statistics have been offered to substantiate the assumption that this physical factor has any etiological bearing in bronchogenic carcinoma" (3519).

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Authors critical of role of tobacco smoke and occupational/ environmental inhalants. The next group of publications were critical of extrinsic factors in general, and appeared to favor host susceptibility. Sweany, from Chicago Municipal Tuberculosis Sanitarium (3445, 3539), was critical of McNally (3224), who coincidentally was also from Chicago:

> "Recently McNally has pointed out that the increase in lung cancer parallels the consumption of cigarettes. This theory is one that offers one of the best explanations that has been suggested up to the present time, because of the close conformity of the lung cancer curve to the increase in the consumption of cigarettes. Nevertheless, more apparent things than that have failed to prove up, so we must wait and see what experiment will bring. If there is any merit in this theory, it should be manifest in the female sex, where the increase in the use of cigarettes has been greater than in men. If, for example, the ratio of men to women twenty years ago was 3 to 1, and now it is 1.5 to 1, the case is well nigh proved. So far, no such increase in ratios has appeared, for the sex ratio was and still is around three males to one female, similar to other malignant conditions other than those of sex differences. On the other hand, there are many patients with lung cancer who do not give a history of cigarette smoking at all.
>
> As other suspected factors are studied, the probability of their relationship to the cause of lung cancer becomes more remote, and in fact many approach the realms of improbability. Such, for example, are the various chronic diseases that have been accused - certain races, smoke, dust, tar, dusty occupations, and many more, none of which when critically analyzed produce more lung cancers than the others, and all have a proportionate quota not having the disease.
>
> After carefully studying the many possible agents accused of causing lung cancer, it seems that only the radium ores can be definitely indicted. But this is an expected result and certainly is in a different category than most other irritants, because radium emanations brutally alter the germ plasm of any germinative cell." (pages 563-564 of ref. 3444)

If McNally could not convert his own colleagues in Illinois, it was not surprising that New Yorkers ignored him. Hochberg & Lederer, from New York Jewish Hospital, stated in their article on "Early Manifestations of Primary Carcinoma of the Lung":

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"Numerous theories have been advanced as to the bearing of inhalation of dusts or of tar from roads as a possible etiologic factor in carcinoma of the lung. No evidence of any such connection has ever been proved. Nor have tuberculosis, influenza, tobacco and war gases been shown to be etiologic agents." (page 81 of ref. 3929)

Passey and Holmes, from the University of Leeds, in their study on the incidence of intrathoracic neoplasia in the teaching hospitals of Great Britain, discussed the contribution of occupational/environmental inhalants:

"It is agreed by most writers that cancer of the lung is more common in the male. This higher incidence in males is claimed by some to be of aetiological importance, and in consequence some writers have attempted to find in our modern mode of life factors which might bring about this difference in sex incidence. The two most recent prominent changes in our mode of living which have been slected in support of their claim are the great increase in smoking and the use of the motor-car. The first as an aetiological factor has received no support from work in the laboratory. If in reality this was the main determining cause of the so-called increase in lung cancer, how can the supporters of this theory explain the fact that cancer of the tongue, larynx and pharynx have not increased in proportion to the increase which they claim to detect in the case of the lung, which, after all, is the last part of the respiratory tract to be exposed to its influence?

The case against the motor-car is supported by two schools, composed of those who think the pollution of the air of our narrow streets by exhaust fumes is the determining factor and those who blame the tarring of the roads. The former hypothesis has nothing whatever to support it. No one has yet shown that garage hands are specially prone to lung cancer. If tarring of the roads is a responsible factor there has never been demonstrated any susceptibility to lung cancer in taxi-drivers, tram, or motor-omnibus drivers and conductors, or in those who drive commercial vehicles or act as chauffeurs. Is there any evidence of a higher incidence in the thousands of men who tend our roads, or in those members of the Police Force of the Automobile Association and the Royal Automobile Club, whose daily occupation is to stand on duty at points of traffic concentration and at cross roads where it is reasonable to expect that suspension of road dust in the air would be at its maximum?

Tarring of the roads did not become general in this country until the War period, whereas the rise in the lung-cancer incidence, which some profess to see in Duguid's table, shows itself as early as 1901-5 and is firmly established by 1911-15. The accompanying Table VII given by Bridge and Henry in a communication dealing with industrial cancers shows that workers in the indust-

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> ries closely connected with tar and other allied carcinogenic compounds require an exposure under fairly intimate circumstances for very long periods before cancer, mostly of the cutaneous surfaces, first appears.
>
> It is reasonable to expect that lung cancer, if induced by inhalation of tar-contaminated road dust, would require at least as long a latent period before making its appearances. Campbell (3453) has recently shown that the exposure of mice to an atmosphere highly contaminated with a sample of road dust, containing 2 per cent. of tar, is capable of inducing malignant tumours of the skin. It is significant, however, that up to the time of the publication of his article he had completely failed to induce primary lung cancer, although the experiments had been in progress for more than a year, whereas the first skin tumour appeared in six months. By analogy it seems reasonable to expect that the inhalation of tarry dust would take longer in producing tumours of the lung in men than such frequent application of tar to the skin as occurs in the tar and allied industries referred to in the Table. Thus, if indeed there be anything in this hypothesis, it is certainly not reasonable to expect lung tumours in man, in any numbers, for some years yet to come. In short, tarring of the road has not been in progress for a sufficient length of time to produce the changes in the incidence of lung cancer which many claim they can detect by their statistical methods, especially those who find this increase commencing in the pre-war or early post-war years." (pages 334-335 of ref. 3537)

Passey and Holmes were critical of tobacco smoke and tar particulates probably because they could not find any increase in lung cancer incidence. It should be noted that Passey and Holmes treated the two as separate causative factors, i.e., personal exposure versus occupational/environmental exposure.

Authors who mention tobacco, coal tar and host susceptibility. More than 400 articles on clinical aspects of lung cancer were examined for the preparation of this chapter. Most of them (90 percent) did <u>not</u> mention tobacco smoke as a causative factor. The following articles, mostly case reports, mention tobacco, coal tar and host susceptibility in the list of causative factors. The authors did not comment whether they believe in the tobacco causation. It is interesting that smoking habits of the lung cancer

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patients were not included in case reports, even though the introduction alluded to the theory of tobacco smoking as a causative factor. The relevant articles derived from the 400 lung cancer articles are as follows:

Bib. No.	Authors	Geographic Location
(3011)	Bonner	Georgia
(3715)	Pierce & Ingersoll	Michigan
(3729)	Donald	Michigan
(3113)	Allen & Smith	Michigan
(3030)	Goltz	Michigan
(3223)	Tyler	Nebraska
(3526)	Neely	Nebraska
(3930)	Howes	New York
(3119)	Menne, Bisaillon & Robertson	Oregon
(3831)	Warmolts	Pennsylvania
(3532)	Smith	South Carolina
(3416)	Jermain	Wisconsin
(3446)	Ellis	Manchester (Great Britain)

The above table concludes the survey of publications in response to the question: What was the prevalent opinion on the cause of cancer? About 90% of lung cancer authors did not believe tobacco smoking was an etiologic factor to be investigated or even mentioned in monographs, review articles or clinical publications. Under Topic D, the acceptance of occupational/environmental exposure as important etiologic factor is reviewed for the same decade.

Prevalence of Cigarette Smoking in Lung Cancer Patients.

Harris' Table 2 included articles that supported the "preposition that cigarette smoking caused cancer." There were nine articles dating from 1927 to 1936; the 1937 article by Ahlbom related largely to oral cancer; and the 1939

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articles by Ochsner & DeBakey and by Müller are reviewed in Chapter IV because critical reservations were expressed during the 1940's.

I composed the following table of scientific articles dated from 1903 to 1938 on the prevalence of cigarette smoking in lung cancer patients. Nine were copied from Harris' Table, whereas 22 entries were from my own manual search of the literature.

(Bib. Number) Author, Geographic Location	Entry in Harris' SOA Table 2 Case Material/Clinical Observation
(0943) Musser (PA)	Clerk, smoked moderately, drunk tea and coffee
(0945) Packard (NY)	Cigar maker
(1611) Scott & Forman (?)	Four gave history of excessive tobacco smoking
(1711) Packard (NY)	Cigarmaker
(1811) Packard (NY)	Cigarmaker
(2117) Friedman (NY)	Smoker, had scarlet fever
(2215) Dana & McIntosh (NY)	German cook; also cigarette smoker
(2319) Folsom (D.C.)	Cigarette smoker; merchant, had typhoid fever
(2421) Seyfarth (Germany ?)*	Quoted Brinkman & Engel's report of lung cancer in cigar smokers
(2615) Perry (DC)	Cigarette smker, had adult whooping cough
(2622) Bel (LA)	Cigarette smoker, contracter
(2711) Perret (LA)*	Harris: "Review of 6 cases of cancer within chest cavity. All 4 of the lung cancer cases for which smoking histories were available reported 'excess use of tobacco'. Although fully realizing that our series of cases is too small to draw any general conclusions, we have been struck by the excessive smoking of many of the patients, and that all the cases occured in males."
(2719) Tylecote (GBR)*	Harris quoting Tylecote: 'I have no statistics with regard to tobacco but I think that in almost every case I have seen and known of the patient has been a regular smoker, generally of cigarette.' (see also DMA page 84)
(2925) Hunt (CAN)	Cigarette smokers: 20 M and 6 F (?)
(2931) Lickint (GER)*	Harris: "Review of laboratory and clinical evidence on tobacco and cancer. Rise in cigarette use linked to rise in lung cancer."
(3031) Mertens (GER)*	Harris: "Increased incidence of lung cancer linked to tobacco. Shift in cancer from oral sites to lower respiratory tract linked to shift from pipes and cigars to inhaled cigarettes."
(3131) Hoffman (MA)*	Harris: "Analysis of San Francisco Cancer Survey. Review of nation-wide vital statistics. 'I

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	am strongly inclined to think that the increase [in lung cancer] is directly connected with the much wider spread of cigarette smoking habits, including the inhaling of smoke which must enter the lungs to a considerable extent in many cases.' 'The observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette smoking habits.' 'Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticable.' 'The increase of cancer of the lung observed in this and many other countries is in all probability to a certain extent directly traceable to the common practice of cigarette smoking and inhalation of cigarette smoke. The latter practice unquestionable increase the danger of cancer development.'
(3212) Rogers (CA)	"Irritating fumes of any sort, with the possible exception of tobacco, did not seem to play a role; 72 percent of this group (50) were smokers."
(3215) Vinson (MN)	Less than half of patients (32) were smokers; only a few smoked to excess.
(3222) Brockbank (GBR)*	"In my series nine (15 per cent) smoked excessively, six smoked thick twist, whilst thirteen (21 per cent) never smoked at all."
(3224) McNally (IL)*	Harris: "Review of chemical constituents of cigarette smoke and their biological effects. 'Comparing the enormous consumption of cigarettes in 1925-1931 with the increase in pulmonary cancer, one is certainly led to believe that cigarette smoking is an important factor in the increase of cancer of the lungs.' 'The tar of cigarette smoke contains nicotine, phenolic bodies, pyridine bases, and ammonia, irritants which could account for cigarette cough, the chronic bronchitis of the cigarette smoker, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung.'
(3327) Pilcher & Brindley (TX)	"In our series it is interesting to note that five of the eight men patients were heavy smokers of cigarettes, although this may not be greater than any selected group of men."
(3540) Thys (BEL)*	Harris: "Review of etiology of cancer. Observed shift in cancer incidence from oral cavity to lung explained by the change from noninhaled pipes and cigars to inhaled cigarettes. 'En conclusion, il

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	noussemble legitime de faire un rapproachement entre le cancer bronchique, cancer des fumeurs d'apres-guerre, et al vogue de la cigarette. Cette notion complete simplement celle des classiques qui imputent a la pipe le cancer labial et lingual, vieille forme du cancer des fumeurs.'
(3603) Craven (NY)	"Claim have been made, both for and against the etiological role of tobacco smoking in cancer of the lung. In 48 male patients with cancer of the lung who gave a statement about their use of tobacco, 31 or 64 per cent were classed as having smoked to excess. In 10 instances this history of heavy smoking was associated with the factor of an occupation that was probably irritation, in 3 instances with a history of repeated or severe respiratory infections, and in 4 instances with both an occupational factor and a history of respiratory infections. On the whole, these figures do not seem very impressive, and seem almost to call for the assumption of some additional factor of special susceptibility of the bronchi to forms of irritation that are probably present to an almost equal degree in subjects who do not develop cancer of the lung."
(3613) Arkin & Wagner (IL)*	Harris: "135 cases of lung cancer diangosed over 4-year period. 'Ninety percent of all our patients were chronic smokers, and we believe that the inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or bronchioles.'
(3627) Fleckseder (AUS)*	Harris: "Among 54 male cases of bronchial carcinoma, 94.4% smoked and 68.5% were heavy cigarette (as opposed to pipe and cigar) smokers. 'So erklart sich wohl der Umstand, dass unter unseren Bronchialkrebskranken die starken Zigaretten raucher in der Ueberzahl waren, sie bringen eben durch das sogenannte Inhalieren den Tabakrauch in ausreichender Konzentration in die grosse Luftwege, wahrend Zigarren- und Pfeifenraucher den Tabakrauch zumeist nicht so tief einzeihen.'
(3720) Frissell & Knox (NY)	"In our series of cases occupation did not play a significant part. There were no miners in the series and only 3 were engaged in dusty trades - a bricklayer, baker, and fireman. Neither were the habits of the patients of significance, except for the well-nigh universal use of tobacco. One had been a victim of war gas. Ten of the cases were in females, 36 in males."

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